A cost-utility analysis of Amisulpride and Paliperidone in the treatment of Schizophrenia

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ABSTRACT

Background: Schizophrenia is a severe, long-term neurodevelopmental disorder that results in increased morbidity and mortality. Amisulpride and Paliperidone are two antipsychotics used to treat schizophrenia in the UK. This evaluation compares the cost-utility of each drug; no similar research has been conducted in the UK.

Methods: A cost utility analysis was performed looking at the benefits in terms of Quality Adjusted Life Years within one year of the treatment, and the costs in pound sterling, discounted to the 2016/2017 value. This evaluation was from the perspective of the National Health Service, the biggest provider of health within the United Kingdom.

Outcomes: The cost utility analysis found an incremental cost effectiveness ratio of £10,941 per added Quality Adjusted Life Year for using Paliperidone, instead of the more widely used Amisulpride.

Interpretation: This is below the NICE threshold of £20–30,000 per QALY. Hence, it is within reason to suggest shifting diagnostic practices to Paliperidone.

1. Introduction

Schizophrenia is a severe, long-term neurodevelopmental disorder that results in increased morbidity and mortality [1, 2]. The Stress Diathesis Theory suggests that it is triggered by pre-existing physical, genetic, psychological and environmental factors that work in combination with raised cortisol levels; however, the exact cause remains unknown [3,4].

The fifth edition of the Diagnostic and Statistical Manual and Mental Disorders (DSM – 5), defines schizophrenia as the co-occurrence of at least 2 symptoms with 6 months of functional decline [1, 5]. The diagnosis of schizophrenia requires the consideration of several factors, such as the familial and social contexts [1, 3].

Schizophrenia is managed with psychosocial rehabilitation and antipsychotics. Patients presenting with a psychotic episode commence antipsychotic treatment for at least one year, followed by lifetime treatment at minimal dose. Antipsychotics have been divided into first (FGAs) and second (SGAs) generation antipsychotics. While FGAs are cheaper than SGAs, they are associated with an increased occurrence of tardive dyskinesia and exacerbation of negative symptoms. Generally, FGAs are not recommended as first-line treatment for schizophrenia. SGAs have a lower risk of extrapyramidal side effects. The better side-effect profile of SGAs must be weighed against their own side effects of weight gain, and increased risk of metabolic syndromes [1].

The choice of antipsychotic ultimately lies between the physician and the patient. The considerations to make are the benefits and side effects, impact on lifestyle and possible drug/alcohol interference. Patients commonly follow varied drug courses; hence, regular follow-up is key [6].

2. Design

2.1. Motivations and rationale

Affecting roughly 1% of the population worldwide [7], 220,000 patients are being treated for schizophrenia within the NHS at any given time [8]. Patients are up to 2.5 times more likely to die due to physical illness associated with the disease [9]. In 2012, 30% of the NHS budget

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on adult mental health and social care was consumed by schizophrenia [7]. Its costs to society due to the loss of productivity and working power, calculated to be £30,000 (for those aged 15–44) and £19,078 (those aged 45 and over) adding up to a total cost of over £5 billion [9].

Despite its significant impact, up to 25% of those diagnosed can become disease-free with early and effective treatment [1, 7]. There is little information on the cost-utility of each of the drugs licensed and used by the NHS. A thorough understanding of the difference in cost-utility can either justify this current practice or suggest a change in prescription habits. It can reduce the already overwhelming cost of schizophrenia in the NHS, while also helping patients be treated more effectively.

We aim for this study to be different in the medications it analyses, and contribute to the literature in providing rationale for choosing a specific medication over the other. There is currently no comparative study of these two drugs in the UK, and this study will aim to guide future prescribing policy.

This study was performed as part of the authors' Health Economics module during their Management BSc at the Imperial College Business School.

2.2. Choice of perspective and analysis

For this study the data on costs, probability values and utility values ere sourced to best serve the perspective of the National Health Service (NHS). The analysis aims to help maximise the use of the allocated NHS budget, and as the health outcomes used are measured in non-monetary terms a cost-utility analysis was conducted.

The advantage of performing a CUA over a CEA is that the latter uses measures of effectiveness that are cruder than utility, such as simply length of life. A CUA uses QALYs as units, adjusting the life gained from an intervention for the quality of the life it adds. This gives a more holistic idea of the benefits of each drug analysed. Since both societal and direct costs vary directly in relation to the quality of the treatment provided, an analysis of the utility of each of the drugs is very appropriate and this can be performed using utility data derived from the Quality Adjusted Life Years (QALYs) that are gained from the use of either Amisulpride and Paliperidone.

A QALY provides a means of comparison that considers both quantity and quality of life years. The quality of life here can be determined in various ways, such as the EQ5D questionnaire which considers depression, discomfort, self-care, activities and mobility. For example, if drug X increases life expectancy by 3 years with a quality value of 0.50 the QALY associated is 1.5. If drug Y gives five years with a quality of life of 0.20, it would give only a QALY of 1.00, despite two extra years.

2.3. Choice of horizon and justification

When comparing the utility of Amisulpride and Paliperidone their individual costs and gains were assessed within the scope of a one-year period beginning with treatment. Indeed, it is important when reading this analysis to be aware that dose reduction, and hence shorter-term usage, often leads to better outcomes than long term use [13]. However, due to a lack of data on the long-term complications for both drugs restricted the scope of the analysis to one year.

In addition, the cost ratio between the two drugs is not expected to change significantly in the subsequent years and the incurred costs are highest in the first year due to a higher rate of relapse [13], thereby providing better rationale for the focus to be on the first year alone.

2.4. Objectives

Between 2003 and 2004, costs for schizophrenia were over £2 billion, excluding the additional indirect costs [10, 11]. It is imperative the NHS makes the best use of this budget. This analysis aims to assess the cost-utility of Paliperidone, one of the newer SGAs, associated with

higher remission rates, better side-effect profile and higher costs. Amisulpride was chosen as a comparator as it is one of the most commonly used antipsychotics in the NHS [12]. This disparity in higher costs yet better benefits calls for a cost utility analysis.

This analysis will provide clinicians with a valuable insight into which of Amisulpride and Paliperidone yields the highest cost-utility. Diligent cost analysis of these two drugs will be needed to answer this question and will add to the current literature surrounding antipsychotic prescriptions to ensure better allocation of resources.

3. Theory

A search of databases PubMed, Google Scholar and Embase using combinations of key search terms "Cost effectiveness analysis", "Cost utility analysis", "cost benefit analysis", "economic analysis", "economic evaluation", "Paliperidone", "Amisulpride", "Atypical antipsychotics", "Second generation antipsychotics" and "Schizophrenia" showed that no cost-utility analysis on the use of Amisulpride and Paliperidone for Schizophrenia has been conducted in the UK.

The search highlighted 17 key papers, 14 of which were shortlisted to source data figures and identify the possible outcomes of both interventions. A cost-effectiveness study comparing the two drugs in Spain [14] was used to obtain the utility values for the initial analysis, while data from three other studies [15, 16, 17] were used to conduct the sensitivity analysis. Probabilities of different outcomes were acquired from NICE [18], while costs of each individual event were collected and calculated from a range of UK studies, reports and international studies [12, 19, 20, 21, 22, 23, 24, 25, 26]. A more detailed outline of the values used in the analysis can be found under "Probability", "Costs" and "Benefits" sections.

All the data was sourced from notable sources or other reliable published and peer reviewed papers. All sources were published within the last decade, except for diabetes costing, data taken from a 2003 paper. To portray the analysis from the perspective of the NHS, all data was specific to the UK except for one figure, where Spanish costing data was used due to a lack of available data [14].

4. Methods

4.1. Probabilities

All the probabilities used in the decision tree were obtained from the systemic review and meta-analysis performed by NICE (Appendix 1) [18]. They are all annual probabilities, presenting the chance of the events taking place within the first 52 weeks of the commencement of the treatment. At every level of the decision tree, the probabilities add up to one, reflecting the underlying assumption that only one of the possible events can occur at any given chance node. Alternative probabilities used in the sensitivity analysis were collected from Lin et al (Appendix 1) [15].

4.2. Costs

Costs have been calculated from the perspective of the NHS. The costs of individual events were either collected from the literature or calculated using available data. All costs are presented/were adjusted to at 2016–17 price levels and converted to pounds where necessary (Appendix 2). The GDP deflator rates used to inflate the costs were obtained from official HM Treasury report published in January 2018 (Appendix 2) [27]. Discounting was not applicable as all the costs were assumed to occur within the first 52 weeks. All the values, calculations and literature used can be found in Appendix 3.

4.2.1. Diabetes

The yearly cost of diabetes was calculated using 2010–2011 UK data from Diabetes UK [22]. This figure includes the cost of screening, testing, treatment and management of diabetes excluding any additional costs

associated with potential complications. In our model, this cost was applied to all diabetes patients, regardless of the complications that they may be experiencing.

4.2.2. Diabetes complications

The costs of diabetes complications used in our model (i.e. amputation, non-fatal myocardial infarction, non-fatal stroke, ischemic heart disease and heart failure) were collected from Clarke et al. [19] All the figures represent the estimated one-year cost for the year in which the event occurred.

4.2.3. Relapse

The mean one-year cost of relapse per patient was collected from a Pan-European study that applied UK unit costs to the resources used [20].

4.2.4. Clinically significant weight gain

This is defined as a weight gain from baseline of more than 7% per year [21]. Based on expert opinion [14], the yearly cost of weight gain was estimated to be equal to the cost of four GP visits. In 2009, Curtis L [26]. estimated the cost of an average GP visit to be £36; this figure was then inflated, and multiplied by four.

4.2.5. Medications

Calculations made to estimate the annual cost of medication can be broken-down in several steps:

1. The average NIC (net ingredient cost) per milligram for both medications was calculated using 2016–2017 UK prescription data [12]. There was no need to inflate the value.
2. The standard daily dose of both medications was obtained from the British National Formulary [23, 24]. The daily dose was then multiplied with costs per milligram to obtain the daily cost.
3. The daily cost was then multiplied by 365.25 days to obtain the annual cost of both mediations.

4.2.6. Extra-pyramidal symptoms (EPS)

The management cost of EPS was estimated to be the equivalent to one visit to the outpatient visit plus biperiden 2mg/8h for three months [14]. The cost of outpatient visit was collected from the "Reference cost report 2015–2016" [26]. The cost of biperiden treatment was acquired from García-Ruiz et al. [14] The costs of outpatient visits and biperiden treatment were then added together and used as an estimate of the costs incurred from EPS.

4.3. Benefits

QALYs were calculated by multiplying the health-related quality of life (HRQoL) with the length of life (LoL) (Eq. (1)). These QALY data used are all adjusted for age and gender.

$$QALYs = HRQoL \times LoL \qquad (1)$$

4.3.1. Length of life (LoL)

Since schizophrenia is a chronic condition that can occur at any age, LoL is different for every single patient, depending on their life expectancy and the onset of the disease. However, this study only assesses the benefits of the treatments during the first 52 weeks following the commencement of the treatment. Therefore, LoL value was estimated to be one year.

4.3.2. Health-related quality of life

The health-related quality of life was expressed in utility values. Although these values were adopted from the Spanish study (Appendix 4) [14], they are based on the UK population and accurately represent the HRQoL of British citizens affected by schizophrenia. The utility values at the decision nodes were obtained by back calculating from terminal nodes (Appendix 5). Discounting of HRQoL was not necessary since the study was evaluating effects over 52 weeks. Two other papers containing relevant utilities were identified [15, 16] and their values were used in the sensitivity analysis.

4.3.3. Quality-adjusted life years

$$Amisulpride \quad QALY = 0.7325 \times 1 = 0.7325 \qquad (2)$$

$$Paliperidone \quad QALY = 0.75 \times 1 = 0.75 \qquad (3)$$

4.4. Sensitivity analysis

During the literature review, we identified a few sizeable inconsistencies in probability and utility values. The three values that showed the largest discrepancy were used in the sensitivity analysis to assess their impact on the incremental cost-effectiveness ratio (ICER). The ranges of figures were used in the calculation of ICER to assess if, even with the sensitivity analysis, the ICER is within limits to warrant a change in medication choice. The sensitivity analyses changed the probability of extrapyramidal symptoms from 0.3163 to 0.11 [15]; the probability of remission from 0.799 to 0.919 [16]; and the annual cost of relapse from £9,617 to £27,012 (post inflation) [17]. The effects of the sensitivity analysis are discussed in the discussion. Calculations for these sensitivity analyses are shown in Appendix 7.

5. Results

5.1. Decision tree

See Fig. 1 at the decision node, patients were simulated to receive either Amisulpride or Paliperidone treatment. Due to large pharmacological similarities between the two treatments, further branches are assumed to be the same for both medicines. Due to its complexity, only the outcomes that were considered to have a significant effect on cost-effectiveness were included. The probabilities used in the decision tree reflect the chances of an outcome occurring within the first year of the commencement of the treatment.

Following treatment, the patient is expected to achieve one of the two health states – remission or relapse. Those who have experienced remission can be further divided in four groups – extra-pyramidal symptoms, weight gain, no side-effects, type two diabetes. Those who have developed type two diabetes are subdivided into six different outcomes – controlled, amputation, non-fatal MI, non-fatal stroke, heart failure, ischaemic heart disease. The costs and utility values at the terminal nodes were acquired from literature (Appendices 3, 4).

The values at the decision nodes were obtained by back calculating from terminal nodes, using probabilities acquired from literature (Appendices 5, 6) (Fig. 1).

5.2. Incremental cost-effectiveness ratio (ICER)

The ICER calculates the added cost of an extra QALY, if the treatment is changed (Eq. (4)). It looks at the difference between the costs of two medications, and the difference in the QALY's provided. A threshold is used to assess if an ICER is within limits to shift treatment (Fig. 2).

$$
\begin{aligned}
ICER &= \frac{Cost\ of\ Paliperidone - Cost\ of\ Amisulpride}{Paliperdione\ QALYs - Amisulpride\ QALYs} \\
&= \frac{£2,877.86 - £2,690}{0.75 - 07325} = £12,671.42/QALY
\end{aligned}
\qquad (4)
$$

5.3. Monetary net benefit (MNB) and health net benefit (HNB)

MNB and HNB combine the difference in costs, the difference in outcomes and the assumed willingness to pay threshold to express the net benefits of one treatment over the other in the monetary units and
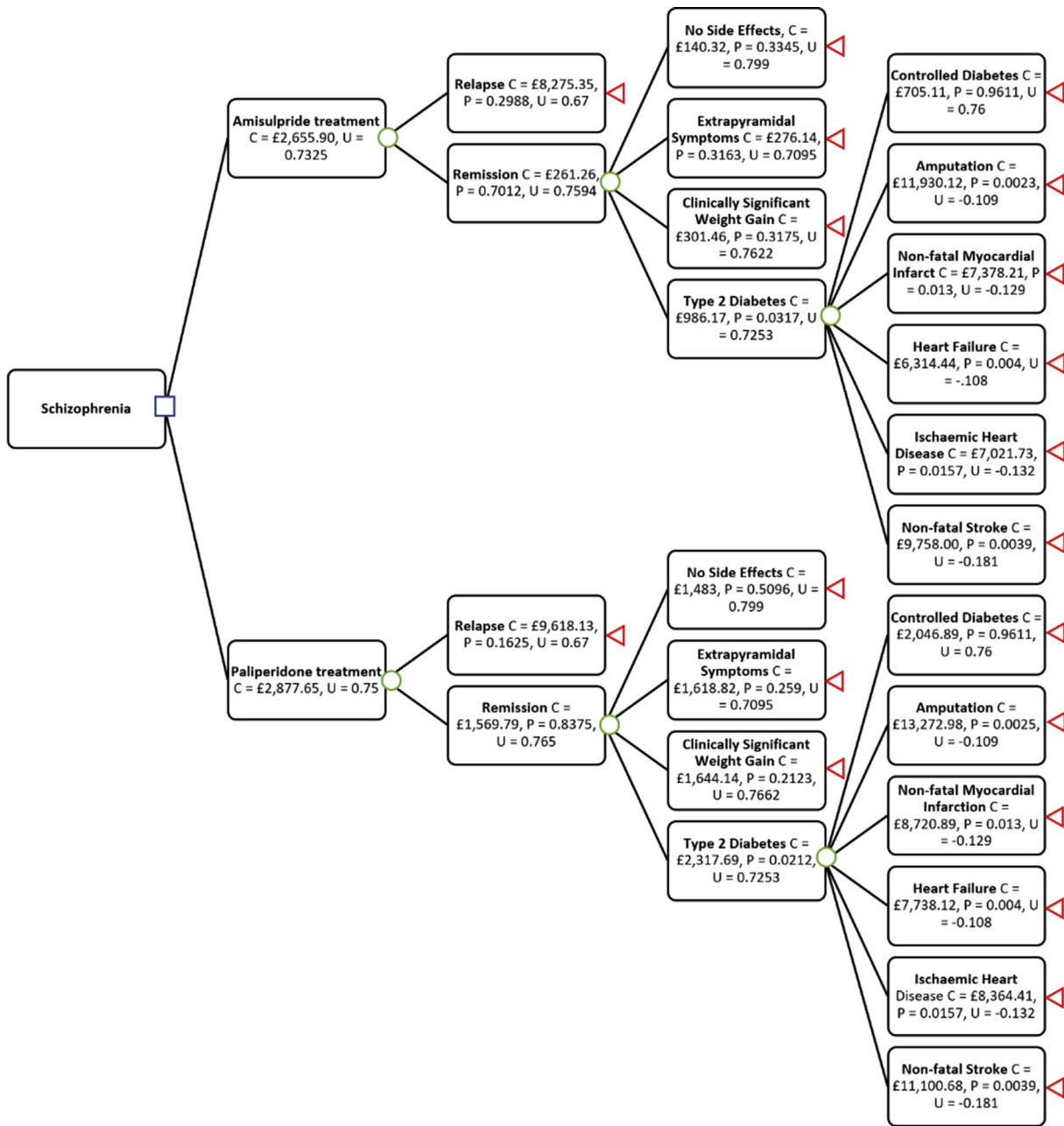
Fig. 1. Decision Tree: shows the associated costs (C), probabilities (P) and utilities (U) for side effects of the treatments Amisulpride and Paliperidone. See Appendices 1, 2, 3, 4, 5, 6 for calculations.

QALYs, respectively (Eqs. (5), (6), (7), and (8)). MNB and HNB were calculated using both the lower and the higher NHS Threshold [28]: Δ refers to a'a change in' where R is the NHS threshold, E is the C is cost, E is the difference in QALYs and C is the difference in overall cost.

$$MNB_{20,000} = (R \times \Delta E) - \Delta C = (£20,000 \times 0.0175) - £221.75 = £128.25$$
$$(5)$$

$$MNB_{30,000} = (R \times \Delta E) - \Delta C = (£30,000 \times 0.0175) - £221.75 = £303.25$$
$$(6)$$

$$HNB_{20,000} = \Delta E - \left(\frac{\Delta C}{Rc}\right) = 0.0175 - \left(\frac{221.75}{£20,000}\right) = 0.0064125 \ QALYs \quad (7)$$

$$HNB_{30,000} = \Delta E - \left(\frac{\Delta C}{Rc}\right) = 0.0175 - \left(\frac{221.75}{£30,000}\right) = 0.10108 \ QALYs \quad (8)$$

5.4. Sensitivity analysis - Results

However, these data should be taken in the context of the sensitivity analyses performed. Firstly, our sensitivity analysis for the probability of extrapyramidal symptoms; while NICE gave this a value of 0.3163 [18], Lin et al found this probability to be 0.11 [15]. This increased the ICER value to £40,034/QALY (Appendix 7), taking it above the NHS threshold [28]. If the latter value proves to be correct, Amisulpride would be the superior option regarding cost utility.

We then applied a sensitivity analysis to the utility of remission. While the value of 0.799 was used [14] Briggs et al determined this to be 0.919 [16]. These changes would see the ICER value fall to £5,420.97 (Appendix 7), strengthening the argument to choose Paliperidone over
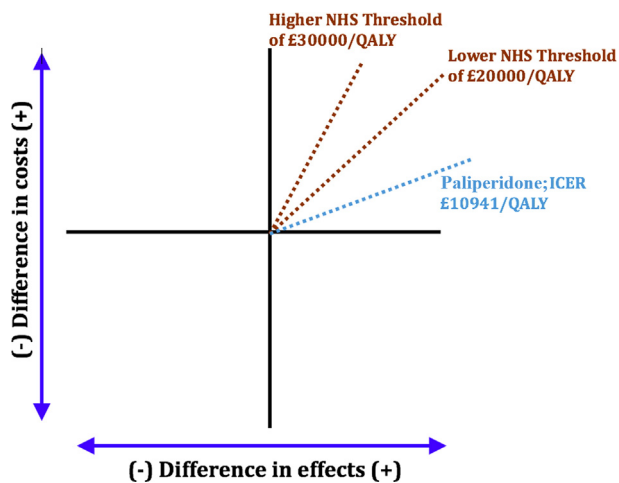
Fig. 2. Cost Effectiveness Plane: showing the position of Paliperidone against the thresholds held by the NHS [28].

Amisulpride.

A third sensitivity analysis was performed due to Munro et al [17] estimating the annual mean cost of relapse to be £27,012. As this is significantly higher than the values used in the initial analysis, a sensitivity analysis was deemed necessary (Appendix 7). In this analysis paliperidone dominates Amilsupride as it costs £2943.73 less and provides 0.0175 more QALYS.

Our last sensitivity analysis was performed to include higher costs of clinical significant weight gain, according to the 2014 NICE guidelines [29]. This estimated an additional cost of £91.00 for a 12 -week course on weight management. Including this cost in the sensitivity analysis saw the ICER value increase by £0.01 to £12,671.43/QALY.

6. Discussion

As the graphs and the ICER show, the use of Paliperidone would require an extra £12,671 for a single extra QALY, below the suggested NHS threshold of £20–30,000 [28]. This suggests that the prescription habits of psychiatrists should begin to shift from Amisulpride to Paliperidone. The issues of equity and environment were beyond the scope of this cost-utility analysis. The authors believe that these issues are unlikely to have a major impact on the decision-making process for these two drugs. This is in line with the studies in Spain and Singapore that came to the same conclusion [14, 15]. This incremental cost-effectiveness ratio should be considered heavily by psychiatrists aiming to make the most cost-effective decisions in an already stretched environment [7].

The monetary net benefit of between £128.25 and £303.25 and the actual health net benefit of between 0.0064125 QALYs and 0.10108 QALYs show that Paliperidone gives a higher utility to the pound than Amisulpride; thus, its rates of prescription should be higher in the UK.

Our results are in line with the current literature, making our findings more reliable. The QALY data used came from a study using the UK population [14], making it more valid to apply it to the UK population in this study.

6.1. Limitations

The main limitations to our study was lack of available data, the fact that not all the side effects could be considered, and that the model did not account for potential discontinuation of medication. Discontinuation of medication can be a result of non-compliance or intolerable side-effects. The discontinuation rate was not factored in due to a lack of utility values. However, discontinuation rates were excluded from both models and there is no reason to suspect that it would differ significantly

between the two drugs.

We also only included the side-effects and diabetes complications that had a major impact on cost-effectiveness in our model. Unfortunately, we had to exclude the impaired glucose tolerance and tardive dyskinesia side effects from the analysis due to a lack of information on their associated costs and QALYs. Additionally, our model assumes a patient would develop just a single side effect whilst multiple side-effects are probable.

Due to a lack of data, the cost of biperiden was acquired from a Spanish study [14]. To account for this, the cost was inflated and converted to pounds, though the actual cost of the drug sourced in the UK might still differ. Again, due to scarcity of information, prescription and dispensation fees were not included in the annual cost of Paliperidone and Amisulpride. However, we can assume that these fees are similar for each drug and would not have a major effect on the overall cost of the treatment.

6.2. Research in context

6.2.1. Evidence before this study

PubMed, Google Scholar and Embase were used to collect data, on 26th February 2018, using the search terms: "Cost effectiveness analysis", "Cost utility analysis", "cost benefit analysis", "economic analysis", "economic evaluation", "Paliperidone", "Amisulpride", "Atypical antipsychotics", "Second generation antipsychotics" and "Schizophrenia". Papers had to be published within the last decade, peer-reviewed, and relevant to the UK population (an exception was made for two papers, one written in 2003, and another from Spain, due to lack of available data).

6.2.2. Added value of this study

This study adds to the pool of data regarding anti-psychotic agents, and their cost-effectiveness. No UK study has been performed on these two drugs, and the study can be used to begin to shift diagnostic practices.

6.2.3. Implications of all the available evidence

This study suggests that diagnostic practices of doctors should begin to shift from Amisulpride to Paliperidone. It also opens the door to further research in performing a network analysis of the antipsychotic agents to improve the current understanding of the cost-effectiveness of anti-psychotic agents.

7. Conclusion

While antipsychotic drugs have been the mainline treatment for Schizophrenia for >50 years, few economic evaluations have been conducted from the perspective of the NHS to date. Current guidelines for prescription are vague, resulting in costly prescription changes, side effects and delays in effective treatment; therefore, CUAs in this area would be of high value to the NHS.

Both medications compared in this analysis are approved by NICE and BMJ as the first-line treatments for Schizophrenia so using one over another would not incur any additional costs. It would be reasonable to argue that Paliperidone should be preferred to Amisulpride as the cost for the additional QALYs are lower than the NHS threshold values. However, in 2016, 405,509 packs of Amisulpride were prescribed, compared to 1,644 packs of Paliperidone [12]. The authors believe that a larger, more detailed study is needed to further assess the superiority of Paliperidone over Amisulpride and other first-line drugs used for Schizophrenia.

Declarations

Author contribution statement

A. Abdall-Razak: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools

or data; Wrote the paper.

A. Macaulay: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

J. Tiefenbach: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

K. Borges, S. Mathema, S. Zuberi: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

Appendix

Appendix 1. Probability Values

A '-' denotes a value irretrievable from the sources.

<u>Amisulpride</u>

Complications	NICE, 2009	Lin et al.
Relapse	0.2988	0.33
Extrapyramidal Symptoms	0.3163	0.11
Weight Gain (> 7%)	0.3175	0.22
Controlled Diabetes	0.9611	-
Type 2 Diabetes	0.0317	0.04
Amputation	0.0023	-
Non-Fatal Myocardial Infraction	0.0130	-
Non-Fatal Stroke	0.0039	-
Heart Failure	0.004	-
Ischemic Heart Disease	0.0157	-
No Side-Effects	0.3345	-

<u>Paliperidone</u>

Complications	NICE, 2009	Lin et al.
Relapse	0.1625	0.25
Extrapyramidal Symptoms	0.2569	0.23
Weight Gain (> 7%)	0.2123	0.21
Controlled Diabetes	0.9611	-
Type 2 Diabetes	0.0212	0.03
Amputation	0.0023	-
Non-Fatal Myocardial Infraction	0.0130	-
Non-Fatal Stroke	0.0039	-
Heart Failure	0.004	-
Ischemic Heart Disease	0.0157	-
No Side-Effects	0.5096	-

Appendix 2. Inflation Appendix

A '-' denotes a value irretrievable from the sources.

Event	Costs Acquired from the Literature	The Year the Cost Was Estimated	Inflation Rate (Calculated Using HM Treasury Report) (3.s.f.)	Inflated Cost
Relapse	£7,270	2009–2010	100/89.346 = 1.119	£8,135.13
Outpatient Visit	£117	2015–2016	100/97.86 = 1.022	£119.57
Biperidene	£15	2011–2012	100/92.289 = 1.0835	£16.25
Clinically Significant Weight Gain	£144	2009–2010	100/89.346 = 1.119	£161.14
Type 2 Diabetes	£513.54	2010–2011	100/90.979 = 1.099	£564.89
Amputation	£8,459	2002–2003	100/75.353 = 1.327	£11,225.09
Non-Fatal Myocardial Infraction	£5,104	2002–2003	100/75.353=1.327	£6,673
Non-Fatal Stroke	£6,822	2002–2003	100/75.353=1.327	£9,052.79
Heart Failure	£4,227	2002–2003	100/75.353=1.327	£5,609.23
Ischemic Heart Disease	£4,760	2002–2003	100/75.353=1.327	£6,316.52
No Side-Effects	£0	-	-	£0.00
Paliperidone	£1,483/year	2016–2017	-	£1,483
Amisulpride	£140.32/year	2016–2017	-	£140.32

Appendix 3. Cost Break-Down

A '-' denotes a value irretrievable from the sources.

Costs of Individual Events

Individual event	Inflated Cost	Source
Relapse	£8,135.13	Paper 7
Extrapyramidal Symptoms	£135.82	Paper 1, 13
Clinically Significant Weight Gain (> 7%)	£161.14	Paper 12
Type 2 Diabetes	£564.89	Paper 8
Amputation	£11,225.09	Paper 6
Non-Fatal Myocardial Infraction	£6,673	Paper 6
Non-Fatal Stroke	£9,052.79	Paper 6
Heart Failure	£5,609.23	Paper 6
Ischemic Heart Disease	£6,316.52	Paper 6
No Side-Effects	£0.00	-
Paliperidone	£1,483.00	Paper 9, 10
Amisulpride	£140.32	Paper 9, 11

Costs of Terminal Nodes - Amisulpride

Terminal Node	Formula	Final Cost of The Terminal Node
Relapse	Relapse + Amisulpride	£8,275.45
Extrapyramidal Symptoms	EPS + Amisulpride	£276.14
Clinically Significant Weight Gain (> 7%)	Weight gain + Amisulpride	£301.46
Controlled Diabetes	Type 2 diabetes + Amisulpride	£705.21
Amputation	Type 2 diabetes + Amisulpride + Amputation	£11,930.12
Non-Fatal Myocardial Infraction	Type 2 diabetes + Amisulpride + Non-fatal MI	£7,378.21
Non-Fatal Stroke	Type 2 diabetes + Amisulpride + Non-fatal stroke	£9,758.00
Heart Failure	Type 2 diabetes + Amisulpride + Heart failure	£6,314.44
Ischemic Heart Disease	Type 2 diabetes + Amisulpride + Ischemic heart disease	£7,021.73
No Side-Effects	Amisulpride	£140.32

Costs of Terminal Nodes - Paliperidone

Terminal Node	Formula	Final Cost of The Terminal Node
Relapse	Relapse + Paliperidone	£9,618.13
Extrapyramidal Symptoms	EPS + Paliperidone	£1,618.82
Clinically Significant Weight Gain (>7%)	Weight gain + Paliperidone	£1,644.14
Controlled Diabetes	Type 2 diabetes + Paliperidone	£2,047.89
Amputation	Type 2 diabetes + Paliperidone + Amputation	£13,272.98
Non-Fatal Myocardial Infraction	Type 2 diabetes + Paliperidone + Non-fatal MI	£8,720.89
Non-Fatal Stroke	Type 2 diabetes + Paliperidone + Non-fatal stroke	£11,100.68
Heart Failure	Type 2 diabetes + Paliperidone + Heart failure	£7,738.12
Ischemic Heart Disease	Type 2 diabetes + Paliperidone + Ischemic heart disease	£8,364.41
No Side-Effects	Paliperidone	£1,483.00

Appendix 4. Utility Values

A '-' denotes a value irretrievable from the sources.

Individual Event	García-Ruiz et al.	Lin et al.	Paper 3)
Relapse	0.67	0.67	0.604
No Side-Effects	0.799	0.8	0.919
Extrapyramidal Symptoms	0.7095	0.72	0.722
Clinically Significant Weight Gain (> 7%)	0.7662	0.77	0.825
Controlled Diabetes	0.76	0.77	-
Amputation	-0.109	-	-
Non-Fatal Myocardial Infraction	-0.129	-	-
Non-Fatal Stroke	-0.181	-	-
Heart Failure	-0.108	-	-
Ischemic Heart Disease	-0.132	-	-

Appendix 5. Decision Nodes Utility

A '-' denotes a value irretrievable from the sources.

Amisulpride

Decision Node	Calculation	Utility
Type 2 Diabetes	P(Amputation) x U(Amputation) + P(Non-Fatal MI) x U(Non-Fatal MI) + P(Non-Fatal Stroke) x U(Non-Fatal Stroke) + P(Heart Failure) x U(Heart Failure) + P(Ischaemic Heart Disease) x U(Ischaemic Heart Disease) + P(Controlled Diabetes) x U(Controlled Diabetes) = (0.0023 x -0.109) + (0.013 x -0.129) + (0.0039 x -0.181) + (0.004 x -0.108) + (0.0157 x -0.132) + (0.9611 × 0.76) = 0.72529	U = 0.72529
Remission	P(No side-effects) x U(No side-effects) + P(EPS) x U(EPS) + P(Weight gain) x U(Weight gain) + P(T2D) x U(T2D) = 0.3345 × 0.799 + 0.3163 × 0.7095 + 0.3175 × 0.7662 + 0.0317 × 0.7253 = 0.7594	U = 0.7594

(*continued*)

Decision Node	Calculation	Utility
Amisulpride Treatment	P(Relapse) x U(Relapse) + P(Remission) x U(Remission) = $0.2988 \times 0.67 + 0.7012 \times 0.7594 = 0.7325$	U = 0.7325

Paliperidone

Decision Node	Calculation	Utility
Type 2 Diabetes	P(Amputation) x U(Amputation) + P(Non-Fatal MI) x U(Non-Fatal MI) + P(Non-Fatal Stroke) x U(Non-Fatal Stroke) + P(Heart Failure) x U(Heart Failure) + P(Ischaemic Heart Disease) x U(Ischaemic Heart Disease) + P(Controlled Diabetes) x U(Controlled Diabetes) = $0.0023 \times -0.109 + 0.0130 \times -0.129 + 0.0039 \times -0.181 + 0.004 \times -0.108 + 0.0157 \times -0.132 + 0.9611 \times 0.76 = 0.72529$	U = 0.72529
Remission	P(No Side-Effects) x U(No Side-Effects) + P(EPS) x U(EPS) + P(Weight Gain) x U(Weight Gain) + P(T2D) x U(T2D) = $0.5096 \times 0.799 + 0.2569 \times 0.7095 + 0.2123 \times 0.7662 + 0.0212 \times 0.7253 = 0.41 + 0.18 + 0.16 + 0.015 = 0.765$	U = 0.765
Paliperidone Treatment	P(Relapse) x U(Relapse) + P(Remission) x U(Remission) = $0.1625 \times 0.67 + 0.8375 \times 0.765 = 0.75$	U = 0.75

Appendix 6. Decision Nodes Costs

Decision node	Calculation	Utility
Type 2 Diabetes	p(AM) x c(AM) + P(NFMI) x C(NFMI) + P(NFS) x C(NFS) + P(HF) x C(HF) + P(IHD) x C(IHD) + P(CD) x C(CD) = 0.0023 x £13272.98 + 0.013 x £8720.89 + 0.0039 x £11100.68 + 0.004 x £7738.12 + 0.0157 x £8364.41 + 0.9611 x £2047.89 = £2317.69	C = £2,317.69
Remission	P(NSF) x C(NSF) + P(EPS) x C(EPS) + P(WG) x C(WG) + P(T2D) x C(T2D) = 0.5096 x £1483 + 0.2569 x £1618.82 + 0.2123 x £1644.14 + 0.0212 x £2317.89 = £1569.79	C = £1,569.79
Paliperidone Treatment	P(REL) x C(REL) + P(REM) x C(REM) = 0.1625 x £9618.13 + 0.8375 x £1569.79 = £2877.65	C = £2,877.65

Decision node	Calculation	Utility
Type 2 Diabetes	p(AM) x c(AM) + P(NFMI) x C(NFMI) + P(NFS) x C(NFS) + P(HF) x C(HF) + P(IHD) x C(IHD) + P(CD) x C(CD) = 0.0023 x £11390.12 + 0.013 x £7378.21 + 0.0039 x £11930.12 + 0.004 x £7378.21 + 0.0157 x £7021.73 + 0.9611 x £705.21 = £986.17	C = £986.17
Remission	P(NSF) x C(NSF) + P(EPS) x C(EPS) + P(WG) x C(WG) + P(T2D) x C(T2D) = 0.3345 x £140.32 + 0.3163 x £276.14 + 0.3175 x £301.46 + 0.0317 x £986.17 = £261.26	C = £261.26
AmilsuprideTreatment	P(REL) x C(REL) + P(REM) x C(REM) = 0.2988 x £8275.45 + 0.7012 x £261.26 = £2655.90	C = £2,655.90

Appendix 7. Sensitivity Analysis

A '-' denotes a value irretrievable from the sources.

1. Probability of extrapyramidal symptoms in patients treated with Amisulpride was assumed to be 0.11. The difference between the value used in the initial analysis and this value was added to "No side-effects" outcome.

Calculation

Decision node	Calculation	Utility and Costs
Type 2 Diabetes	This change does not affect the "Type 2 diabetes" decision node	-
Remission	P(NSF) x C(NSF) + P(EPS) x C(EPS) + P(WG) x C(WG) + P(T2D) x C(T2D) = 0.5408 x £140.32 + 0.11 x £276.14 + 0.3175 x £301.46 + 0.0317 x £986.17 = £75.88 + £30.38£ + £95.71 + £31.26 = £233.23 P(NSF) x U(NSF) + P(EPS) x U(EPS) + P(WG) x U(WG) + P(T2D) x U(T2D) = $0.5408 \times 0.799 + 0.11 \times 0.7095 + 0.3175 \times 0.7662 + 0.0317 \times 0.7253 = 0.776$	Costs – £233.23 Utility – 0.776
Amisulpride Treatment	P(REL) x C(REL) + P(REM) x C(REM) = 0.2988 x £8275.5 + 0.7012 x £233.23 = £2,636.26 P(REL) x U(REL) + P(REM) x U(REM) = $0.2988 \times 0.67 + 0.7012 \times 0.776 = 0.744$	Costs – £2,636.26 Utility – 0.744

Impact on ICER

ICER = Cost of Paliperidone - Cost of Amisulpride/QALYs of Paliperidone - QALYs of Amisulpride = £2,876.47£ - £2,636.26£/0.75 QALY - 0.744 QALY = £40,034.00/QALY

2. Utility value of "No-side effects" chance node was assumed to be 0.919.

Amisulpride

Decision node	Calculation	Utility And Costs
Type 2 Diabetes	This change does not affect the "Type 2 diabetes" decision node	-
Remission	P(NSF) x U(NSF) + P(EPS) x U(EPS) + P(WG) x U(WG) + P(T2D) x U(T2D) = $0.3345 \times 0.919 + 0.3163 \times 0.7095 + 0.3175 \times 0.7662 + 0.0317 \times 0.7253 = 0.798$	Utility – 0.798
Amisulpride Treatment	P(REL) x U(REL) + P(REM) x U(REM) = $0.2988 \times 0.67 + 0.7012 \times 0.798 = 0.759$	Utility – 0.759

Paliperidone

Decision node	Calculation	Utility and Costs
Type 2 Diabetes	This change does not affect the "Type 2 diabetes" decision node	-
Remission	P(NSF) x U(NSF) + P(EPS) x U(EPS) + P(WG) x U(WG) + P(T2D) x U(T2D) = $0.5096 \times 0.919 + 0.2569 \times 0.7095 + 0.2123 \times 0.7662 + 0.0212 \times 0.7253 = 0.828$	Utility – 0.828
Paliperidone Treatment	P(REL) x U(REL) + P(REM) x U(REM) = $0.1625 \times 0.67 + 0.8375 \times 0.828 = 0.8$	Utility – 0.8

Impact on ICER

ICER = Cost of Paliperidone-Cost of Amisulpride/QALYs of Paliperidone-QALYs of Amisulpride = £2,877.86 - £2655.90/0.8 QALY - 0.759 QALY = £5,420.97/QALY

3. The cost of relapse was assumed to be £27,012.00. The costs of medicines were also added to represent the overall cost of "relapse" outcome

Amisulpride

Decision Node	Calculation	Utility and costs
Type 2 Diabetes	This change does not affect the "Type 2 diabetes" decision node	-
Remission	This change does not affect the "Remission" decision node	-
Amisulpride Treatment	P(REL) x C(REL) + P(REM) x C(REM) = $0.2988 \times £28,495.00 + 0.7012 \times £261.26 = £8,697.71$	Cost - £8,697.71

Paliperidone

Decision Node	Calculation	Utility and costs
Type 2 Diabetes	This change does not affect the "Type 2 diabetes" decision node	-
Remission	This change does not affect the "Remission" decision node	-
Paliperidone Treatment	P(REL) x C(REL) + P(REM) x C(REM) = $0.1625 \times £27,152.32 + 0.8375 \times £1,563.92 = £5,753.98$	Cost - £5,753.98

Impact on ICER

ICER = Cost of Paliperidone - Cost of Amisulpride/QALYs of Paliperidone - QALYs of Amisulpride = £5753.98 - £8697.71/0.75 QALY - 0.7325 QALY = -£168,213.14/QALY

4. The cost of weight gain management was assumed to be £252.14.

Amisulpride

Decision Node	Calculation	Utility and costs
Type 2 Diabetes	This change does not affect the "Type 2 diabetes" decision node	-
Remission	P(NSF) x C(NSF) + P(EPS) x C(EPS) + P(WG) x C(WG) + P(T2D) x C(T2D) = $0.3345 \times £140.32 + 0.3163 \times £276.14 + 0.3175 \times £392.46 + 0.0317 \times £986.17 = £352.26$	C = £352.26
Amilsupride Treatment	P(REL) x C(REL) + P(REM) x C(REM) = $0.2988 \times £8275.45 + 0.7012 \times £352.26 = £2746.90$	C = £2,746.90

Paliperidone

Decision Node	Calculation	Utility and costs
Type 2 Diabetes	This change does not affect the "Type 2 diabetes" decision node	-
Remission	P(NSF) x C(NSF) + P(EPS) x C(EPS) + P(WG) x C(WG) + P(T2D) x C(T2D) = $0.5096 \times £1483 + 0.2569 \times £1618.82 + 0.2123 \times £1735.14 + 0.0212 \times £2317.89 = £1660.79$	C = £1,660.79
Paliperidone Treatment	P(REL) x C(REL) + P(REM) x C(REM) = $0.1625 \times £9618.13 + 0.8375 \times £1660.79 = £2968.65$	C = £2,968.65

Impact on ICER

ICER = Cost of Paliperidone - Cost of Amisulpride/QALYs of Paliperidone - QALYs of Amisulpride = £2,968.65 - £2,746.90/0.75 QALY - 0.7325 QALY = £12,671.43/QALY

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